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CONTENTS

E D I T O R I A L

JUSTICE OR TREASURY DEPARTMENT FOR NARCOTIC CONTROL?

THE recent legislative proposal which would place the Bureau of Narcotics in the Department of Justice rather than the Treasury Department has met with unified and forceful opposition in every area of pharmacy. The reasons for this opposition are not difficult to understand.

Over the years the relationship between the Bureau of Narcotics, as it is currently administered, and pharmacy has been most cordial and cooperative. Pharmacists have been treated with consideration and professional respect, and they in turn have conformed to the provisions of the Harrison Act to a degree which has been in most cases exemplary. The officers in the Bureau have maintained their contacts with pharmacists not as police officers but as helpful colleagues, anxious and willing to interpret the law and help pharmacists carry out the responsibility vested in them. This does not mean that the narcotics officers could not and would not get tough when the need arose. They did not, however, approach pharmacists with that air of suspicion and distrust all too common among typical police officers. The result has been that the entire personnel of the Bureau from Commissioner Anslinger down has been, and is, the friend of pharmacy. In many respects it is the dignity and philosophy of Commissioner Anslinger which has been instilled in the ranks of the Bureau. This is indeed a tribute to him as a man as well as an administrator. Pharmacists are loath to see one of the few relationships concerning which they have no complaints changed. They are not at all sure that change would, or even could, be for the better and this with all respect to the Department of Justice.

There has, of course, been a growing public concern over the problem of drug addiction, particularly as it affects our children and young adults. This is indeed a problem but it is at times over-

emphasized by lurid stories in newspapers which give it great publicity, as they do murders—publicized often far beyond its true significance in order to sell papers. In this problem the pharmacist plays almost no role whatsoever since it is indeed rare for a pharmacist to act as a source of illicit narcotics. Even those stolen from pharmacists are but a trickle in the stream of illicit supply.

Anyone truly familiar with the problem of drug addiction knows that the simple transfer of the responsibility for law enforcement to the Justice Department will not bring a solution. The basic and underlying cause may be found in those social evils which cause juvenile delinquency in the first place, and its varied sequelae of crime and violence. Drug addiction, chronic alcoholism, wanton murder and all other such critical problems are symptoms of a sick society brought on by slums, parental irresponsibility, poor schools and a lessened respect for both God and temporal authority. Even the F. B. I. cannot cope with this nor will increased punishment for violators go far in bringing it under control.

Our national lack of concern in the education of our children, effective slum clearance, and all similar basic social needs is at the root of the problem and these must be attacked. More punishment and more police will not get at the source of the trouble.

We are, however, of the opinion that the Bureau of Narcotics deserves more financial support than it gets. Its task is truly stupendous when one considers the vast boundaries of the United States and how easy it is to smuggle in illicit drugs. Surely, public sentiment would endorse doubling the Bureau's present budget so that its good work could be expanded. These men know their business and understand the narcotics problem well. Congress should think carefully before reorganizing this respected government bureau and placing it under another administrative head. There is no easy way to solve the narcotics problem and a change is not necessarily an improvement. Pharmacists are convinced that the change proposed would be an unhappy and ill-advised move and they will oppose it on every front.

L. F. Tice

DRUGS FOR A CHANGING WORLD *

By Joseph B. Sprowls **

ALTHOUGH it is admittedly difficult for one who is historically minded to evaluate the period during which he lives, I feel certain that future historians will look back upon our present generation of Western civilization not only as the founders of the atomic era but also as a group who have made unprecedented advances in the area of medical sciences. No other corresponding period in history has seen so many laboratories, man hours, and millions of dollars devoted to studies of the causes of disease and the quest for better methods or agents for the prevention or mitigation of the illnesses which plague mankind. The requirements for the certification of new products which have been established by the Federal Security Administration under the authority of the Food and Drugs Administration Act have brought about a close cooperation between this agency of the government, the pharmaceutical industry, and the health professions. Research teams have been developed having a wide range of backgrounds and interest, and a keen spirit of competition has developed in the search for useful medicinal products. The pharmaceutical industry deserves considerable recognition for the comparatively large percentage of annual income which is budgeted for research and development. A recent report indicates that a total of more than one hundred million dollars yearly are budgeted for such purposes. The constant flow of new finished pharmaceuticals has become the lifeblood of the industry and has brought inestimable benefits to the health of the public.

Until twenty-five years ago the major emphasis in pharmaceutical research was upon the admixture of ingredients of known therapeutic virtue in an attempt to discover new methods of use or more successful combinations. Since the outstanding successes of the sulfonamides and antibiotics, however, the emphasis has shifted to a search for totally new agents either of natural or synthetic origin having more powerful or more specific activity than anything heretofore recognized. The new approach has already been remarkably successful—so successful, in fact, that it can now be predicted with some degree of cer-

* Presented at the University of Buffalo Inauguration Exercises for Chancellor Clifford Cook Furnas, January 7, 1955.

** Dean, School of Pharmacy, Temple University.

tainty that pharmacology will soon emerge from its shackles of empiricism and become a more or less exact science. One can see patterns emerging which point the way toward a chemical or physical chemical basis for this science which in the past has had to proceed through the slow and tedious method of trial and error.

So many advances have been made in therapeutics in recent years that it is impossible to mention them all; however, it will be the purpose of this paper to survey some of the most significant trends of drug research which have emerged during recent years and to superimpose some chemical mediation upon the whole.

In the field of autonomic drugs, for example, great strides have been made through systematic screening of promising synthetic compounds. It is here that we find our most convincing arguments for a chemical approach to pharmacology. Adrenalin (epinephrine) and acetylcholine have been recognized as the chemical mediators of the autonomic nervous system since the fundamental experiments of T. R. Elliott in 1904 and of Otto Loewi beginning in 1921; however, it was not until 1934 that Dale elaborated a completely acceptable hypothesis to explain the functions of the autonomic system in terms of "cholinergic" fibers and "adrenergic" fibers. This hypothesis has served as a very useful tool for the coordination of a great deal of information which relates to the activity of various autonomic drugs and in the devising of experiments for the further advancement of our knowledge.

Since many disease symptoms arise from a temporary imbalance of the autonomic functions, it has been useful to restore this balance either through augmenting the functions of one of its divisions or through blocking the functions of the other. Of the two possibilities greater success has usually attended the blocking procedures. Hence, we have seen the introduction of a succession of improved blocking agents for epinephrine and acetylcholine. Because acetylcholine functions both at parasympathetic endings and at autonomic ganglia, inhibitors of acetylcholine have received major attention.

Outstanding successes have been achieved in the development of agents which block acetylcholine at parasympathetic nerve endings (parasympatholytics). These drugs are particularly useful in relieving the pain and discomfort which accompany gastric ulcer and a host of other conditions which are associated with hyperirritability of the gastro-intestinal tract. Early drugs in this series such as adiphenine and amprotropine were not highly effective, but the recent discovery

that quaternization of the amino nitrogen enhances the intestinal anticholinergic activity has not only improved the usefulness of the drugs but has also given rise to the suggestion that a close similarity to the natural agent may be an important requirement for successful antagonism. The significance of this statement may be seen by examining the formulas for a number of parasympatholytic agents including the mildly effective tertiary amines, adiphenine and amprotropine, and the much more successful methantheline, diphenmethanil methylsulfate, and tricyclamol.

One group of the parasympatholytics (cholinergic blocking drugs) have been moderately successful in relieving peripheral vascular disorders of a spasmodic nature; however, the results thus far have been far from satisfactory and one may safely say that the ideal antispasmodic for such use remains to be found.

Blocking of acetylcholine at autonomic ganglia has been most satisfactorily accomplished through use of the methonium compounds. These modern descendants of the tetraethyl ammonium, first used by Barger and Dale in 1915, represent two quaternary ammonium groups at either end of a methylene chain of 5 or 6 carbons in length. They have been most widely used in the relief of hypertension, where their greatest disadvantage is the rapid onset and short duration of effect. These failings have made the regulation of dosage and the maintenance of a stabilized blood pressure most difficult. Recently there has been introduced a new drug, pentolinium (Ansolysen), in which the quaternary ammonium groups have been "protected" by cyclizing so that the action is not only enhanced but also prolonged. This may not be the ideal drug for hypertension, but it appears to represent an outstanding advance over the penta- and hexamethoniums and has already been hailed by outstanding authorities as the drug of choice for severe and malignant forms of the disease.

Great interest centers in drugs of all types for administration in hypertension because this condition is perhaps the greatest enemy of our aging population. Statistics show that in 1900 only 13 per cent of our citizens were over 50 years of age, whereas by 1960 this age group will comprise 25 per cent of the total. As life-expectancy is extended still further, the problem of treating diseases of the declining years will grow in importance. Knowledge of this change in the character of the general population has already accelerated research on all types of geriatric drugs.

In addition to the ganglion blocking agents just discussed, compounds have been investigated which can block the pressor activity of the sympathetic neurones. The natural pressor agent activated by these nerves was once thought to be epinephrine, but it is now believed to be the demethylated compound, arterenol. (Indeed, synthetic l-arterenol has been introduced as an agent for use in combatting circulatory emergencies and is recognized as one of the most potent pressor materials known!) Unfortunately, the drugs which reduce blood pressure do not fall into a simple pattern of blocking arterenol as was true with the antagonists to acetylcholine. Some drugs seem to block pressor activity by depressing higher centers. Drugs which exert a blocking effect upon the effector cell are referred to as adrenolytics, sympatholytics, or adrenergic blocking agents.

Recent research has revealed the anti-hypertensive value of the ergot alkaloids which were previously regarded as too dangerous for use. In the form of hydrogenated derivatives the alkaloids ergocornine, ergocrystine, and ergocryptine have been found to be highly effective and safe for use. They are used in a combined form which has been introduced under the trade name Hydergine. A multitude of synthetic adrenergic blocking drugs have been introduced. The list would include phenoxybenzamine, phentolamine, tolazoline, hydrolazine, piperoxan, etc. Continued research will probably yet produce drugs of this group which will be effective and sufficiently free from troublesome side reaction to be notable, but to date none has been outstandingly successful, and they are primarily used as adjuncts to other antipressor agents.

One of the drugs which acts primarily through a blocking of pressor functions in higher centers is the natural drug *Rauwolfia serpentina* and its extracts and alkaloids. This drug is an ancient Hindu remedy which has been recently re-introduced as a result of a more careful study of its utility. It belongs to the mild group of hypertensive drugs and is only useful in simple forms of the disease or in conjunction with more effective compounds; however, the drug gives promise of having significance far beyond its value in circulatory disease. It has been found to have outstanding value in the treatment of mental disease. Because of its calming effect upon patients, it has proven of value in apprehensive states and mental delusions. Used either alone or in combination with chlorpromazine it may lower the admissions to mental hospitals and allow more mental patients to

be released from hospitals earlier. It has also been stated that the combination with chlorpromazine will improve the welfare of the aged, both because it will relieve the mental tension which often accompanies advancing years, as well as offer protection against the sequelae of hypertension.

Closely related to hypertension is the condition, arteriosclerosis, which begins to threaten many persons after they have entered the fourth or fifth decades of life. Although arteriosclerosis may develop in the person with normal arterial tension, it occurs with even greater frequency and degree in persons suffering from hypertension. One of the forms of arterial degeneration which takes place in the early form of the disease is the deposition of lipoid plaques in the intima of the elastic arteries, which condition is referred to as *atherosclerosis*. It is the formation of these plaques which is believed by some to precede most cases of coronary infarction and coronary occlusion. Much presumptive evidence indicates that the lipotropic drugs are useful in preventing the formation of the atheromatous plaques, and this accounts for the current interest in preparations containing choline, betaine, methionine, inositol and beta-propiothetin, all of which are believed by some to have value in the metabolism of lipoids. Geriatric formulations are already making use of these compounds in the belief that they will yet be proven to be of value in preventing the development of atherosclerotic and arteriosclerotic conditions.

It should be noted that several vitamins are believed to serve various functions in maintaining the health of the circulatory system; hence, the geriatric formulas also make great use of this group of physiologic substances, in particular thiamine, niacin, ascorbic acid, and the tocopherols.

Mention has been made earlier of the methonium compounds. It is interesting to observe that if the carbon chain in these molecules is extended to ten carbons, the resultant drugs have a relaxant effect upon voluntary muscle. This can be explained on the basis of blocking acetylcholine at the nerve endings of skeletal muscle fibers. Just why a bisammonium compound with a methylene chain of 5 or 6 carbons should block acetylcholine at autonomic ganglia and a similar compound with a chain of 10 carbons should block acetylcholine at skeletal muscle sites is not clear. Nevertheless, it appears that the proper spatial distribution of quaternary ammonium groups is significantly related to these activities. The introduction of decamethonium and compounds of a similar structure (succinylcholine, *Anectine*)

plus a reinvestigation of the value of curare alkaloids have brought significant changes in the practice of anesthesia. Many anesthetists are now using muscle relaxants as adjuncts to anesthesia in many types of surgery in order to provide greater flaccidity. The drugs also have utility in reducing injury during insulin or metrazol shock and for the treatment of spastic disorders, as well as for many other purposes.

The antihistamines seem to have almost run the full gamut of possible uses at this stage and have become established as useful primarily for purposes of relieving some symptoms of disease. Their ability to alter the degree or extent of histamine reaction in a multitude of allergic manifestations, drug reactions, and similar conditions has been firmly established, although the claim that they have value in prevention of the common cold seems without proof.. Research with the drugs of the antihistamine type has, however, brought forth a closely-related drug of outstanding interest. This is the drug chlorpromazine (*Thorazine*) which differs from one of the popular antihistamines only in containing a chlorine atom in the ring system and one additional methylene group in the effective side-chain. Central nervous depressant activity has always been notable in the antihistamines. In chlorpromazine the central nervous depressant activity is so unique that the primary action is a calming effect upon the patient without clouding the consciousness or dulling the intellect. This has led to use of the drug in a variety of conditions extending from nausea in pregnancy to the treatment of mental disease. In neuropsychiatry the drug has proven to be an outstanding tool for improving the outlook of a large variety of patients. It brings to many a calm and more rational approach to life than they have previously experienced and may lead to the restoration of some mental patients as useful citizens. The social value of such a drug makes it one of the outstanding contributions of recent years. Mention has previously been made of its use in combination with Rauwolfia.

Significant advances have been made in the study of anticonvulsant drugs. Selective service records for World War II indicated that there were probably about 600,000 epileptics in this country. The estimate has more recently been placed at one million by some writers who have also pointed out the distressing social features of the disease. It is estimated that forty thousand sufferers of the disease are now confined to institutions at a cost to society of eighteen million dollars a year. Added to this consideration is the unfortunate fact that many

sufferers who are not confined to institutions are, nevertheless, not able to hold useful positions because of their physical condition.

Although no drug can be universally successful in epilepsy because of the varied forms in which the disease is manifested, phenobarbital has been the most useful drug in the majority of cases. The chief disadvantage of phenobarbital is its sedative effect which brings about a drowsy condition in the patient. Recent investigations have focused attention upon the methyl barbiturate derivatives, *Mebaral* and *Gemonil*, the methyl hydantoin, *Mesantoin* and the pyrimidine dione, *Mysoline*. These drugs have the value of being anticonvulsant with less pronounced sedation. While further use may indicate that none of these is the ideal compound, they, nevertheless, seem to point the way toward a chemical structure of improved value.

Research attention has also turned to combinations of the anticonvulsants with central nervous stimulants and with skeletal muscle relaxants. Thus, we find appearing on the market such combinations as phenobarbital with desoxyephedrine and phenobarbital with mephenesin. This trend will probably continue until a single compound with ideal properties has been developed.

Sufferers from arthritis have received encouragement from the introduction of cortisone, which has brought dramatic relief in some cases. It is estimated that one person in every twenty is afflicted by this disease, rheumatism, or a related ailment. These, too, are diseases of advancing years, since fourteen per cent of cases of arthritis are in the age group over 65 and an additional 46 per cent of cases are among those betwen 45 and 65 years of age. Arthritis is not only a crippling disease but is often extremely painful as well.

Kendall's Compound E, or cortisone, and the anterior pituitary hormone ACTH have served both to revolutionize the treatment of rheumatoid arthritis and to give us new understanding of the nature of the disease. Kendall's Compound F has now been introduced as hydrocortisone and is superior to cortisone in some respects. Since all of these substances have received such wide publicity, it is not necessary to review their pharmacology at this point. Unfortunately, none of these hormones is free from some objectionable features, and no one of them is beneficial in all cases. For these reasons great activity may be observed in the search for cortisone-like compounds. The major effort seems to be directed along two separate lines: (1) the search for steroids which can be converted to cortisone or to compounds having cortisone activity, and (2) the search for synthetic

materials which have a structure somewhat related to cortisone and having the same type of activity. Researchers interested in the first approach are testing steroids prepared from all manner of sources—the sex hormones, vegetable oil residues, and various plant glycosides. Those interested in the second approach have thus far produced significant compounds from stilbene and hexane and a compound known as decahydronaphthoketol.

Another approach to the relief of pain associated with arthritis and rheumatism has been the development of more effective analgesics than those which have been in common use. The compound Butazolidin was introduced as a result of investigations designed to produce compounds having an action similar to that of aminopyrine without its harmful effects. The drug Tibione originally introduced for the therapy of tuberculosis has been found to have good antiarthritic effects, although the mechanism of action is still uncertain. Relief of pain arising during acute exacerbations has been obtained by using tetraethylammonium bromide. Thus, two new groups of synthetic products are indicated.

The list of diseases for which no specific treatment or preventive method is yet known grows shorter every year. Progress in immunology and chemotherapy has practically removed all fear of infectious disease for those who live in this enlightened age. Those infections, which the vaccines and preventive sera do not control, have been conquered by the antibiotics with the exception of the rickettsial diseases and some of the virus and tropical infections. Only a partial victory can be claimed against tuberculosis, since neither streptomycin nor the newer chemical drugs are fully successful in controlling the disease. Notable among the virus group are those which cause poliomyelitis and the common cold.

While the search for new antibiotics will undoubtedly continue, it appears that chief attention will be directed toward the search for antibiotics having these and other specific values. Meanwhile, two other avenues of antibiotic research have emerged, both of which have chemical significance. One of these is the development of chemical derivatives of the known antibiotics. Natural penicillin is an acid compound which forms salts rather easily. At first only the sodium or potassium salts were used, then it was discovered that a procaine salt gave longlasting properties. More recently compounds have been introduced which have remarkable powers of duration. Thus, benzathine penicillin G (*Bicillin*) appears in the blood stream for 14 days

following an injection of 600,000 units. In addition to its use in the routine treatment of infections, the drug may be regarded as a major contribution in the therapy of venereal disease where its use has become routine in some centers both for prevention and for removal of infection. It has also been reported as outstandingly successful in the treatment of rheumatic fever.

Certainly there is every reason to assume that even more beneficial compounds may yet be produced by alteration of existing antibiotics, and it is rather obvious that research has already been instituted with this objective in view.

Organic chemists take great delight in improving upon nature, both through altering the products of nature, and, where possible, by synthesizing substitutes for the materials provided by nature. Such a beginning has been made in the field of antibiotics. The antibiotic *Chlormycetin* had hardly reached the market before the Parke Davis chemists had devised a method for its synthetic preparation. In the years which have since passed numerous synthetic analogues of the compound have been synthesized and studied. The chemical formula for penicillin has been known for some time and the formulas for aureomycin and terramycin have recently been elucidated. The chemistry of the latter two is remarkably similar. Realizing the manner in which chemists have continously replaced natural products with synthetic organic chemicals which are generally of simpler structure and more economical to manufacture, it is also reasonable to assume that we will eventually have synthetic replacements for the antibiotics. The whole history of modern drug research indicates that this is a probability, and we may be sure that it has not been overlooked by our research laboratories. The problem would seem to be one of the most challenging of those which are current.

Among the chronic problems which has received a more satisfactory solution in the past few monts is that of pernicious anemia. I shall not attempt to review the history of anti-pernicious anemia treatments at this point, but I am certain that all are generally familiar with the concept introduced by Castle in 1929 which indicated that two factors are essential in the prevention of the disease. One of these factors is derived from external sources and is called the extrinsic factor; the other is present in gastric juice and is called the intrinsic factor. While recent discoveries of folic acid and of Vitamin B_{12} have forced us to revise our concept of this theory to some extent, the basic proposition is still useful for this discussion.

Vitamin B_{12} seems to have all of the activity of the extrinsic factor. When administered by injection it seems to have all of the activity of the anti-anemia principle; however, it is not nearly as effective orally (about 1/40th) as it is by injection. If mixed with gastric juice before oral administration it is as effective as when given by injection. Folic acid, on the other hand, seems to be related to the digestive mechanism by which the vitamin B_{12} content of food becomes available. Continuous research on the components of achylia gastrica has now yielded a mucoprotein fraction which gives the activity of the intrinsic factor. When administered simultaneously with vitamin B_{12} the full anti-anemic activity of the vitamin is realized. Thus, a new era in anemia therapy has been launched whereby it is possible to treat pernicious anemia by oral therapy. Examples of the new products which have been made available are the pharmaceuticals *Bifacton* and *Biopar*.

At the same time a better understanding of the part played by folinic acid and vitamin C in the prevention of anemias has made it possible to avoid or more successfully treat some of the nutritional anemias and sprue.

No attempt will be made in this paper to review research in drugs designed for the control of cancer, although many such agents have been developed and studied. At the present time three types of chemicals are receiving major attention: (1) those which act as mitotic poisons, such as the mustargens and triethylenemelamine, (2) those which are antagonists to normal metabolites, such as 2-amino purine and 6-mercaptopurine, and (3) radioactive elements. The inhibitors of metabolism seem to offer greatest promise at the present time, since they usually have a greater margin of safety. The results in the field of cancer drugs have been encouraging but at the present time they must be regarded as very much incomplete.

The studies of antiparasitic and antituberculosis drugs have been ignored, but not because they are lacking in significance. The limitations of time would not permit an exhaustive review of these subjects and to do any less would be an injustice. Suffice it to say, therefore, that new drugs have been developed which have great effectiveness against *Endomeba histolytica*, the malarial parasites, and other parasitic organisms. The antituberculosis drugs, para-aminosalicylic acid and isonicotinyl hydrazide have fallen far short of expectations but have proven themselves as valuable adjuncts to streptomycin and will probably yet point the way to more effective synthetic chemicals.

Although this summary of modern drugs has been brief, it has perhaps served to indicate the breadth of current advances in therapeutics. Medical historians of the future may look back upon us from some superior vantage point and regard our contributions as insignificant, but we, in turn, looking back upon centuries of tedious progress immodestly regard our successes as hardly short of miraculous. Furthermore, the rapidity with which fundamental discoveries are quickly translated into new and effective methods of therapy and the speed with which they are distributed as tested, safe medicinal agents is a credit to the health professions of our nation. Surely, it is proof that the competitive system operates even in the bringing of better health to more citizens, and we as pharmacists can all be proud to be a part of the great system which not only serves to instigate much research but also brings the products thereof to the ultimate consumer with the speed of Mercury and the authority of Apollo.

INHIBITING CANCER IN ANIMALS. V. (1949-53)

By John R. Sampey *

RECENT surveys by the author (133, 134, 135, 136) on inhibiting cancer in animals have covered 475 articles. The present study surveys 170 additional reports for the period, 1949-53.

I. Inorganic Chemicals

Radiolanthanum. La^{140} had marked inhibiting effect on Ehrlich ascites tumor in mice (99). Stable La^{139} showed only minimal inhibition.

Radiostrontium. Sr^{89} inhibited Ewing's sarcoma in mice (120).

Cyanides. Bacq, et al. (4, 62) protected mice against lethal doses of X-rays with sodium and potassium cyanides.

Cyanates and Thiocyanates. Sodium cyanate increased mitosis of ascites carcinoma but thiocyanate was without therapeutic effect (10).

Arsenite. Potassium arsenite injected into mice before the transplantation of leukemic cells inhibited growth at first, but resistance developed in succeeding generations (122).

Minerals. Ash of rat tumors injected near newly transplanted Jensen sarcoma inhibited tumor growth (36). Birch ash and a commercial mixed mineral preparation were without effect on ITB-tumors in rats (158).

II. Organic Nitrogen Compounds

Guanazola. 8-Azaguanine prolonged the lives of mice with lymphatic leukemia (91), and it caused a decreased mitotic rate in carcinomas 755 and Eo771 in mice (167). 8-Azaguanine-2-C^{14} was 100 times as great in susceptible leukemic tumors as in dependent tumors in mice (14). Skipper (147) inhibited mouse tumors and leukemia with a combination of guanazola, amethopterin and DL-thionine. When guanazola was injected one hour after the administration of flavotin it inhibited neoplasms in mice (31).

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Nitrogen Mustard. HN2 given subcutaneously or intraperitoneally showed a destructive effect on Ehrlich ascites carcinoma (152), and given intra-arterially it induced regression in rat tumor 2226 and OVCA tumor (160). Heston (63) reported nitrogen and sulfur mustards caused sarcomas in mice (63). The n-oxide of nitrogen mustard caused marked regression of Yoshida sarcoma (137, 171).

6-Mercaptopurine. This purine destroyed Sarcoma 180 (24, 25), and Ehrlich ascites tumor in mice (152), and it prolonged the lives of mice with lymphatic leukemia (91).

Phosphoramides. Sugiura (152) inhibited Ehrlich ascites carcinoma in mice with triethylene phosphoramide (TEPA), and Sparks, et al. (150), reported all phosphoramides they tested caused remissions in rats with myeloid chloreleucemia. Crossley, et al. (29), claimed even more striking results, reporting TEPA cured 70% of rats with S-231 and 72% cures on rats with Flexner-Jobling carcinoma. Shay, et al. (145), found triethylene thiophosphoramide (thio-TEPA) effective against two types of myelogenous leukemia in rats. McCoy, et al. (145), inhibited adenocarcinoma with TEPA.

TEM. 2,4,6-Triethyleneimino-1,3,5-triazine (TEM) was also effective against lymphomas in dogs (106), Ehrlich ascites tumor in mice (152) and Jensen sarcoma in rats (104). Kravitz, et al. (87), warned against the formation of uric acid crystals under TEM therapy.

6-Thiopurine. Sugiura (151) reported this purine and 1,9-di-(methane sulfonoxy)nonane retarded S-180, C-1025, Ehrlich carcinoma, etc., in rodents.

Thiouracil. Thiouracil accelerated the appearance of MC or benzpyrene tumors in male mice but inhibited growth, while in females the reverse situation was true (13).

Aromatic Amines. Woolley (170) induced regression of mammary tumors in mice with analogs of dimethyldiaminobenzene, while Leiter, et al. (94), damaged S-37 in mice with diphenylamines and aminofluorenes (93).

Urethane and Uracil. Mice infected with grey-lung virus failed to develop malignant changes when given urethane (46). Clarke, et al. (26), inhibited S-180 with urethane. Young mice pretreated with uracil had fewer tumors induced by urethane (130).

Amino Acids. Cysteine has been used to protect against nitrogen mustard injury (163), and x-irradiation injury (121). Thyroxin (13) favored the growth of MC or benzpyrene tumors in male mice but not in females. B-2-Thionyl-dl-alanine inhibited Sarcoma T-241 in mice (69).

Nicotinamide. This compound inhibited DAB hepatomas in rats (84).

N-Methylformamide. S-180 in mice was inhibited with this amide (26).

1,5-Diaminobiuret. Leukemia L-1210, S-180, edenocarcinomas Eo771 and 755 in mice were inhibited by doses of diaminobiuret (70).

D-Glucosamine. This agent retarded S-37 in mice (124).

III. Folic Acid Analogs and Antagonists

Aminopterin prolonged the lives of leukemic mice (47, 48), but it did not alter the rate of growth of Mill-Hall endothelioma in chicks (128). Amethopterin showed a synergistic effect with antimalarial drugs in increasing the survival of leukemic mice (114, 115). Skipper (147) reported that amethopterin combined with DL-ethionine and guanazola inhibited mouse leukemia more than when used alone. Pollak, et al. (122), have described the resistance leukemic mice developed to continued use of amethopterin. Weygand, et al. (165), retarded mouse ascites tumor with 6-aminofolic acid. Brown (22) noted that 2-deaminofolic acid did not inhibit Walker C-256.

IV. Hormones

Androgens. Testosterone kept the livers of hypophysectomized rats free of tumors from azo dye feeding (129). The combined therapy of testosterone and desoxypyridioxine had a carcinostatic effect on mouse breast cancer (143, 144). Transplanted mammary tumors in male mice were inhibited (42), while pellets of testosterone had no effect on the growth of Walker rat C-256 (9).

Estrogens. Estrogens have been employed in the treatment of prostatic carcinoma in mice (32) and guinea pigs (116). Female sex hormones also retarded hepatic tumors in castrated rats (88). Ovarian endocrine function inhibited radiation-induced tumors in mice (72, 74, 75).

Cortisone. Cortisone inhibited mouse leukemia (161, 169), Ehrlich ascites tumor (152), rat adenocarcinoma (1), DAB tumors in mice (34), and benzpyrene carcinogenesis in mice (20, 139). Beck (8) noted that cortisone increased the minimum dose of arsenite required to induce necrosis in mouse S-37.

Adrenals. Beck (8) recorded that adrenal extracts behaved as cortisone in necrosis of S-37 by arsenite. Flemming, et al. (39), inhibited S-37 with adrenal extracts. Willig (166) described the carcinostatic effect of adrenalectomy on Walker rat carcinoma. Adrenalin reduced hemorrhages in primary and transplanted tumors (132).

ACTH. ACTH injected into hyphophysectomized rats fed azo dyes did not develop liver tumors (51).

Hyphophesis. Hyphophysectomy prevented azo dye cirrhosis in rats (52, 127) but it was without effect in benzpyrene induced tumors (173) or Walker rat carcinoma (140). Hyphophysectomy before MC administration reduced tumor development, but surgery had no effect if performed after MC application (45). Moon, et al. (110), noted the absence of neoplasms in hyphophysectomized rats.

Growth Hormone. Phyol delayed the formation of DMBA tumors in mice (35).

Thymus. Kaplan (73) reduced X-ray induced tumors in mice and Law and Miller (89, 90) noted reduced incidence of both spontaneous and MC induced leukemia in thymectomized mice.

V. Miscellaneous Agents

Hydrocarbons. Methylcholanthrene inhibited 3'-methyldimethylaminoazobenzene carcinogenesis in rats (108). Miyayi, et al. (109), studied the carcinogenic effect of AAF induced tumors in rats by MC, DMBA and chrysene. Dibenzanthracene was added as an anticancer agent against implanted round-cell sarcoma in rats (58). Foley (41) noted that MC induced sarcomas which regressed following ligation, caused mice to be immune to further MC administration.

Organic Fluorine Compounds. Fluorobenzene retarded tumor growth in rats (141).

Ketones. p-Hydroxypropiophenone retarded ovarian tumor growth in rats (16), but the ketone was ineffective on Walker rat

C-256 (28). p-Aminopropiophenone protected rats against lethal doses of x-rays (21).

Esters. Myleran, or 1,4-dimethane sulfonyloxybutane, and its series n2 to 10 inhibited Walker rat C-256 (54, 55, 56, 59), and mouse breast tumors (44).

Ascorbic Acid. D-Glucascorbic acid retarded Crocker rat carcinoma and mouse adenocarcinoma Eo771 (148).

Indoleacetic Acid. Baranco (5) retarded sarcoma with this chemical.

Isoalloxazines. Several agents of this class regressed lymphosarcoma implants in mice (64).

Tropolones. Several tropolones damaged S-37 (93) and Yoshida sarcoma (78, 79, 80, 138).

Ethylene Glycol. This polyhydric alcohol protected neoplasms from freezing injury before transplantation (49).

Nicotinamide. This chemical inhibited hepatoma formation in rats fed DAB (84).

Colchicines. Derivatives of colchicine damaged S-37 in mice (92), Ehrlich ascites carcinoma (152), BDA tumors in mice (142), and ascites tumor cells (96).

Ethionine. This agent caused regression of Jensen sarcoma and fibro-sarcoma in rats (98).

Arylmethane Dyes. Fifteen basic and two acid dyes were effective against Ehrlich ascites mice tumors (100).

Steroids. Steroids had no effect on neoplasms from AAF when transplantations of adrenals were made in the spleen of rats (125).

Diet. A high casein, low fat diet retarded carcinogenic action of tannic acid on rat livers (86). DAB tumors were inhibited by 5% acetic acid in the diet (112). Varying the level of minerals in the diet had no influence on spontaneous breast tumors in mice (153). Survival time of mice bearing breast carcinoma was longer on a restricted and low calorie diet (154).

Vitamin T retarded the growth of rats but was without effect on lymphosarcoma in the same (157). Vitamin B_{12} had no effect on Walker carcinoma-sarcoma in rats (40). Calciferol inhibited benzpyrene tumors in rats (131).

Virus. Russian Encephalitis was destructive to S-180 (111), and Virus HST retarded Yoshida tumors in mice (57). Sugiura (149) described five viruses with inhibiting power over mouse leukemia. Ehrlich ascites carcinoma was inhibited by Newcastle Virus (123), Bunyamwera Virus (85, 103), St. Louis Encephalitis (23, 85), West Nile (85), Japanese B (85), and louping ill virus (85).

Tissue Extracts. Mosinger (113) reported that extracts of various organs retarded sarcomas in rats. Ehrlich ascites, Yoshida sarcoma and lympho-sarcoma were inhibited by fractions from ultracentrifugation of small intestines of rodents (15). Extracts of mammalian tissue caused hemorrhagic necrosis of S-37 in mice (146). Cell free extracts of both frozen and unfrozen breast cancers produced tumors (17, 18, 19). Cell free filtrates of spleen pulp induced regression in Brown-Pearce carcinoma in rabbits (118). Dialyzed Ehrlich ascites tumor lost its virulence in mice (97). Darcel (30) noted that chicks inocculated with avian leukosis failed to develop further tumors, and Fink, et al. (38), demonstrated the regression of a second implanted S-621 tumor, following inocculation. S-37 transplants to the brain of guinea pigs caused immune response to later transplants (33). Injections of bone marrow inhibited irradiation injury in mice and guinea pigs (27, 76, 77, 101). Sarcoma I grafts did not survive when guinea pigs were pre-injected with lymphilized guinea pig kidney (71). Guinea pig serum injected in mice with transplanted lymphosarcomas induced regression (82, 83). Urinary extracts retarded S-37 in mice and MC tumors in rats (39). ACS had no effect on several neoplasms in rodents (60, 61).

Spleen Protection. Shielding of the spleen during heavy irradiation increased the survival of mice (66, 67, 68, 102).

Podophyllin. Podophyllin induced regression in Yoshida and MTK-sarcomas in rats (107). Podophyllotoxin damaged sarcoma in animals and patients (2).

Plants. Belkin, et al. (11, 12) employed various plant materials to damage S-37 in mice. Leaves and ointment of *aloe vera* hastened healing of lesions from Sr^{90} irradiation (105). Taylor, et al. (155, 156), retarded mouse breast tumors with plant extracts. A phytoagglutinin from the white navy bean had no effect on Flexner-Jobling carcinoma *in vivo* (117).

Enzymes. Arginase was ineffective on mouse neoplasms (50), but Vrat (162) reported this enzyme almost completely destroyed mammary adenocarcinoma in mice. Irons and Boyd (65) noted 28% reduction in the growth of mouse mammary carcinomata after arginase injection. Lettre (95) inhibited mouse ascites tumor with glucose oxidase containing catalase.

Antibiotics. Actinomycin decreased the rate of mitosis of several neoplasms in mice (53). Reilly, et al. (126), reported only 5 of 1200 antibiotics retarded the growth of S-180 in mice. Bateman and Klopp (6) noted that aureomycin prolonged the life of mice with acute leukemia, and they used actidione for treating patients with lympho-, adeno-and epidermoid carcinomas. Ambrus, et al. (3), recorded negative results in the effect of a broad spectrum of antibiotics on tumor inducing virus.

Nitromin. This agent inhibited DAB carcinogenesis in rats (81).

Antimalarials. A combination of antimalarial drugs and amethopterin was effective against mouse leukemia (114, 115).

Yeast. This agent was ineffective in retarding rat sarcoma and mice carcinoma (7).

Ethionine. This agent induced regressions in Jensen sarcoma and fibro-sarcoma in rats (98).

Citrals. Several derivatives of citral that had no free aldehyde groups failed to inhibit Yoshida hepatomas (119).

Malaria. Rous tumor was retarded by injections of plasma from chickens with malaria (159).

Acinin Berna. Mice treated prophylactically with this agent, and later inocculated with Ehrlich tumor lived longer (164).

DNA. Urethane lung adenomas were fewer in mice given Na-desoxyribonucleic injections (130).

Antimetabolites. A number of these agents caused regression of mouse breast tumors (168).

Lithospermum. This agent induced diestrus reduced the incidence of mammary cancer in mice (172).

Age. Rous sarcoma regressed in 15% of adult or old chickens, but never in 15 day old chicks (43).

Ligation. Ligation of spontaneous breast carcinoma in mice failed to give immunity (37).

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A STUDY OF THE PYROGEN CONTENT OF HOSPITAL DISTILLED WATER *

By William B. Swafford ** and W. Lewis Nobles ***

THE parenteral route for the administration of drugs is so widely used today that its basic principles should be familiar to everyone concerned with clinical problems. This should be particularly true of the hospital pharmacist who manufactures parenteral solutions. Regardless of the apparatus used, or the type of solution prepared, there is no excuse for untoward reactions following the administration of injections (1).

Parenteral solutions are a class of sterile pharmaceutical preparations intended for injection under or through one or more layers of the skin or mucous membrane (2). The United States Pharmacopeia, with reference to such preparations, states: "They must be packaged in containers which will maintain the sterility of the liquid or suspension" (3).

Shortly after the use of injectable solutions was introduced it was noted, in many cases, that the injection of salt solutions into man and/or experimental animals, produced a fever (4, 5). If distilled water alone were injected, the same result might be obtained (6). In 1910, Hort demonstrated that the injection of small quantities of water into animals produced this effect (7). Because of the fever produced, the causative agent was designated as pyrogens. The term literally means "fever producers". Of all the problems encountered in the preparation of parenteral solutions, none has attracted more attention or caused more trouble than those associated with the presence of pyrogens.

The present study was concerned with the determination of the pyrogen content of the freshly distilled water of the hospitals in Memphis, Tennessee, the total solids content of this water, and the

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type of still used in preparing it. This study was undertaken in an effort to: (1) determine if the freshly distilled water of these hospitals is pyrogen-free and (2) establish the correlation, if any, between the total solids and pyrogenic content.

In spite of all that has been determined about pyrogens our knowledge of them at present is far from complete. For example, the chemical composition of pyrogens has not been definitely established (8). Pyrogens are probably by-products of bacterial metabolism. They were once believed to be protein-like substances, but are now regarded as complex polysaccharides linked to another radical containing phosphorus and nitrogen (8). They are apparently closely related to bacterial antigens. This conclusion is based on the fact that they undergo many reactions characteristic of the antigens (9-13). One fact about pyrogens has been definitely established: they occur only in media which have been contaminated with bacteria or other microorganisms.

When injections of Salvarsan in saline began to be widely used, it was soon observed that fever might occur after injection. In 1911, Wechselmann (14) found that the use of freshly distilled water in preparing Salvarsan injections eliminated the chills and fevers which had previously been closely associated with these injections.

Hort and Penfold (15) confirmed these findings in the same year. They found that intravenous injections of distilled water, which had been properly preserved, caused no such symptoms. Nevertheless, the intravenous injection of the same water after incubation in non-sterile vessels produced a febrile reaction. Since this fever-producing principle was not removed by passing this water through a Berkefeld filter, these workers postulated that the fever-producing principle was closely associated with bacteria, but was not a part of the bacteria. In 1923, Seibert (16, 17) demonstrated conclusively the bacterial origin of pyrogenic material. Later, Seibert and Bourn (18, 19) studied twenty-five strains of bacteria from various samples of distilled water and found, in each case of those producing fever, that the etiological factor was a filterable, thermostable, desiccation-resistant exotoxin produced by various organisms capable of growing in distilled water. The contamination of distilled water was shown to be due to airborne bacteria and/or a pyrogen exotoxin carried from the raw water in the still pot through the condenser into the distillate. Distillation in a still designed to prevent entrainment, immediate sterilization after distillation, and sealing to protect sterility were

suggested as essential steps in providing water safe for use in parenteral solutions.

CoTui and co-workers (20-26) found that pyrogens could be adsorbed on Seitz asbestos filters and estimated that the pyrogenic particles were between 50 millimicrons and one micron in size.

Untoward reactions following the injection of sterile distilled water containing pyrogens are suggestive of protein shock. In milder cases a moderate fever is observed. The temperature reaches a peak and returns to normal within six hours following the injection. In the more severe cases, hyperpyrexia follows chills or pain in the back or legs and usually occurs while the injection is still flowing. Nausea, vomiting, and diarrhea may ensue. Also, a drop in blood pressure may be noted. In the case of a very serious reaction a marked drop in blood pressure is associated with cyanosis and/or circulatory collapse which may result in death. Mild reactions are distressing to the patient, severe reactions are dangerous, particularly since indications for this form of therapy may present a patient already in a critical condition.

There are seemingly but two prerequisites for a supply of water safe for use in parenteral solutions. They are: (1) a source of pure raw materials and (2) centralized responsibility for cleanliness in the preparation of solutions and apparatus. Any hospital where major surgery is performed has the necessary sterilizing equipment and the trained personnel to whom such responsibility can be delegated (27). The most frequent source of pyrogens in parenteral solutions is probably the solvent. In most cases this is distilled water.

Discussion

As a result of the tremendous importance that pyrogens may have in the preparation of parenteral solutions, the authors became interested in studying samples of distilled water obtained from various sources in an effort to determine whether or not pyrogens were present. Eleven hospitals in the vicinity of Memphis, Tennessee, were selected for the study. Not all these hospitals prepare their own parenteral solutions. For the purposes of this study, however, this was not a primary factor. Of the eleven hospitals in the survey, eight were producing distilled water which proved to be pyrogen-free. Only three of the stills tested were producing water which gave a

positive test.[1] Each of the samples also was tested for its total solids content. The over-all average of total solids content was 0.9 p.p.m. This is far below the tolerance limit of 30 p.p.m. allowed by the U. S. P. for Water for Injection (28). One of the stills showing a positive test for pyrogens gave water having a total solids content of 0.2 p.p.m. This was the lowest content of total solids in water from the eleven stills tested. The readings ranged from 0.2 to 5.6 p.p.m. for this determination. The water sample giving this high reading of total solids gave a negative test for pyrogens. Water from the other two stills giving a positive pyrogen test had a total solids content of 0.3 and 0.5 p.p.m. respectively.

It would appear from these results that there is no direct correlation between the total solids content and the pyrogenic content of freshly distilled water.

The stills tested were of varying age and type. Three were electrically heated; the remaining eight were heated by steam. All the stills utilized the municipal water supply. This raw water had a total solids content of 101 parts per million.

The distilled water from one of the electrically heated stills showed a positive pyrogen test. Two of the steam heated stills produced water which gave a positive pyrogen test. All the stills tested contained baffle plates or other mechanical means of preventing contamination of the distilled water with the raw water.

Experimental

The pyrogen test was conducted according to the official U. S. P. pyrogen test method (29).

The following precautions were taken at all times:

1. The animals were maintained on a uniform diet of Sorno rabbit pellets and water throughout the experiments.

2. Food was withheld from the animals from two hours before the experiment began until the completion of all the temperature readings.

3. All the rabbits used weighed at least 1500 Gm. and not more than 2250 Gm.

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1. In one of these hospitals a leak was found in the condenser of the still which allowed the raw water to mix with the distilled water. This leak was corrected and the water then gave a negative pyrogen test.

4. The rectal temperature of the animals before the experiments ranged from 38.0° to 39.8° C.

5. The dose of distilled water was 10 cc./Kg.

6. All the experiments were run at one-week intervals on female rabbits. Approximately twenty rabbits were available at all times and were used interchangeably.

On the day that the test was to be run, a sterile 100 cc. flask was filled with the freshly distilled water from the still to be studied. The flask, stoppered with a rubber stopper which had been treated for pyrogens, was taken directly to the laboratory where the water being tested was injected into the rabbits. Prior to filling, each flask was thoroughly rinsed with the water that was to be tested.

Immediately before making the injection, a temperature reading was taken on the rabbit. The rabbit was then secured in a box designed to hold the animal during the test period. This was done as quietly as possible to prevent the rabbit from becoming excited, which would automatically bring about a rise in temperature.

By means of a 22-gauge needle the injection was made into the marginal vein of the ear. After the injection was completed, the time of completion was recorded and the rabbit returned to its cage. Injection into the remaining rabbits followed quickly. At the end of each hour for three hours the rectal temperature of each rabbit was recorded. If none of the animals showed an individual rise in temperature of more than 0.6° above normal, the water was considered to be non-pyrogenic. If only one animal showed a temperature rise of 0.6°, or more, the test was repeated using five animals. The same was true if there was a total rise of 1.4°, or more. On occasion the rise in temperature could be attributed to the rabbit's becoming excited. However, if there was any doubt as to the cause of the results obtained, the test was repeated.

The water was used just as it came from the still. No attempt was made to make it isotonic since this would have brought other possible sources of contamination into the picture.

The total solids content was determined by the use of a Barnstead Purity Meter. One hundred cc. of the water being tested was used for this determination. The conductivity cell of the purity meter, which is immersed in the sample being tested, was rinsed with this

water. This insured against possible contamination by pyrogenic exotoxins or solid material which might have dried on the glassware. Once this was done, the total solids determination was merely a matter of temperature determination, adjusting the temperature dial, and observing the "indicator eye tube". It is essential to keep the water and equipment free from contamination. A minute amount of material can produce a change in the determination.

Table I indicates the final results of the tests.

TABLE I

Hospital No.	Type Still	Water Source	Total Solids Determination	Pyrogen Content
1	Barnstead Steam Heat	City	0.3 P.P.M.*	Negative
2	Barnstead Auto Electric Heat	City	0.4 P.P.M.	Negative
3	Barnstead Auto Electric Heat	City	0.6 P.P.M.	Negative
4	Steam Heat Amer. Ster. Co.	City	0.9 P.P.M.	Negative
5	Barnstead Steam Heat	City	0.4 P.P.M.	Negative
6	Barnstead Steam Heat	City	0.3 P.P.M.	Negative
7	Barnstead Steam Heat	City	0.3 P.P.M.	Positive
8	Barnstead Steam Heat	City	0.2 P.P.M.	Positive
9	Barnstead Steam Heat	City	5.6 P.P.M.	Negative
10	Cons. Machine Co. Electric Heat	City	0.5 P.P.M.	Positive
11	Steam Heat Amer. Ster. Co.	City	0.4 P.P.M.	Negative

* Parts per million.

As an indication of the data recorded, Tables II, III, and IV are listed and give the information for the three stills which were producing water which was not free from pyrogens. In like manner data were obtained for the remaining eight stills which were producing pyrogen-free water.

TABLE II

			Pyrogen content:			Positive
Animal No.	Normal Temp.	Injection Completed	1st Reading	2nd Reading	3rd Reading	Total Rise
34	39.66°	12:16	40.06°	40.45°	40.22°	0.56°
36	39.39°	12:31	39.94°	40.06°	40.22°	0.83°
35	39.50°	12:45	40.16°	40.34°	40.06°	0.84°

Total solids content 0.3 parts per million. Barnstead Still. Steam heated.

TABLE III

			Pyrogen content:			Positive
Animal No.	Normal Temp.	Injection Completed	1st Reading	2nd Reading	3rd Reading	Total Rise
22	39.55°	10:10	40.11°	40.28°	40.22°	0.73°
37	39.21°	10:40	39.55°	39.25°	39.55°	0.34°
38	39.13°	10:55	39.78°	39.89°	39.89°	0.76°
43	39.50°	11:10	39.55°	39.55°	39.50°	0.05°
41	39.25°	11:25	39.66°	40.45°	40.28°	1.20°

Total solids content 0.2 parts per million. Barnstead Still. Steam heated.

TABLE IV

			Pyrogen content:			Positive
Animal No.	Normal Temp.	Injection Completed	1st Reading	2nd Reading	3rd Reading	Total Rise
43	39.72°	12:30	40.11°	40.56°	40.45°	0.84°
41	39.72°	12:56	41.33°	41.84°	42.06°	2.34°
40	39.55°	1:12	41.33°	41.67°	41.11°	2.12°

Total solids content 0.5 parts per million. Consolidated Machine Company Still. Electrically heated.

Summary

The freshly distilled water from eleven hospitals in the vicinity of Memphis, Tennessee, was tested for pyrogen content and total solids content.

Of the eleven hospitals cooperating in this study, three were producing distilled water which contained pyrogens.

The totals solids content of all the samples tested was well within the tolerance limit allowed by the U. S. P. for Water for Injection.

Acknowledgments

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SELECTED ABSTRACTS

The Role of PVP in Pharmaceuticals and Cosmetics. Shelanski, H. A., Shelanski, M. V., and Cantor, A. *Am. Perfum. & Essen. Oil Rev.* p. 267 (Oct. 1954). Polyvinylpyrrolidone (PVP) has been found to be a compound of extremely low toxicity. Its potential usefulness in the pharmaceutical and cosmetic fields thus needs full investigation. It has been found to possess the properties of solubilization, desensitization, detoxification, and substantivity having particular application.

As an example of its solubilizing property, PVP forms an iodine complex with elemental iodine which is more soluble. Various other compounds ranging from basic elements to saccharides and proteins have been found to be more soluble in water in the presence of PVP. It has also been found that PVP prevents separation of cosmetic preparations by acting as a suspending agent for substances which it does not carry into solution.

The desensitizing action of PVP was illustrated by the authors by stating that the irritant properties of sodium alkyl sulfonate was reduced in the presence of PVP when tested by the repeated insult patch test technique. Similar results were obtained with the majority of over 100 compounds frequently used in cosmetic formulations.

The toxicity of iodine is reduced from an approximate LD_0 of 150 mg./Kg. to 1500 mg./Kg. when combined with PVP to form the complex. Other compounds which have been found to be reduced in toxicity with PVP are mercury, nicotine and cyanide.

The property of substantivity may be considered as a special type of irreversible adsorption. This phenomenon was illustrated by the penetration and fixation of PVP into the lumen of hair shafts. When the hairs were subsequently washed the PVP could not be removed. Its presence in the lumen of the hair could be shown by chemical test. The appearance of the hair also improved, giving more color and accentuated clarity.

The authors concluded that PVP acts primarily like a protein except that it does not possess the undesirable properties such as the allergenic, antigenic, or depressor releasing effects.

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